ATTACHMENT 5

TOXICITY PROFILES FOR COPCs

INTRODUCTION

This attachment contains toxicity criteria and toxicity profiles for the chemicals selected as chemicals of potential concern (COPCs) for the Pownal Tannery Superfund Site baseline human health risk assessment. The chronic oral and inhalation toxicity criteria for COPCs are summarized in Tables 5.1, 5.2, 6.1 and 6.2. Table 1 presents the absolute oral bioavailability factors (i.e., oral to dermal adjustment factors) used to adjust the oral toxicity criteria for the COPCs evaluated in the dermal exposure pathways, as discussed in Section 4.0, subsection 4.3. Toxicity profiles for the COPCs are provided in the following pages.

VOLATILE ORGANICS

Benzene

Benzene is a clear, volatile, highly flammable, aromatic hydrocarbon which exists naturally and is produced by volcanoes and forest fires. Benzene is also a very common industrial solvent, produced from petroleum. It is used as a solvent for fats, inks, paints, plastics, rubber, in the extraction of oils from seeds and nuts, in photogravure printing, as a chemical intermediate and in the manufacture of detergents, explosives, pharmaceuticals and dyestuffs. It is also a component of gasoline and other petroleum-based fuels. Exposure to benzene can occur via inhalation, ingestion, especially of contaminated drinking water, and dermal contact (as in contact with liquid benzene found in gasoline) (Sittig, 1981; ATSDR, 1997).

Benzene is readily absorbed through ingestion, moderately absorbed through inhalation and poorly absorbed through intact skin. Once in the bloodstream, benzene is distributed throughout the body, with the concentration in any one compartment dependent on the degree of perfusion of tissues by blood. Since benzene is lipid-soluble, it accumulates in fat, but the rate of accumulation is slow since fat is poorly perfused. The metabolites of benzene are responsible for its toxic effects. These include phenol (which is either formed via an unstable benzene oxide precursor or directly from benzene), catechol, hydroquinone and conjugated phenolic compounds. The primary site of benzene metabolism is the liver via the cytochrome P450 mixed function oxidase system. Some benzene metabolism may also occurs in the bone marrow via the same enzyme system. Benzene is excreted either unchanged from the lungs or as metabolites in the urine (ATSDR, 1997).

Benzene targets its effects on the hemopoietic, immune and nervous systems (ATSDR, 1997). Exposure to benzene has produced irritation of the skin, eyes and upper respiratory tract. Acute exposure has produced central nervous system depression, headache, dizziness, nausea, convulsions, coma and death at extremely high concentrations (Sittig, 1981). Health effects in humans have been reported starting as low as 50 ppm via inhalation. Twenty-five ppm for 6 hrs had no obvious effects though benzene was detected in blood (Sandmeyer, 1981). Early autopsy reports found benzene-induced hemorrhages of the brain, pericardium, urinary tract, mucous membranes and skin (Sittig, 1981). Chronic exposure to benzene produces blood changes involving an initial increase in levels of erythrocytes, leukocytes and thrombocytes, followed by aplastic anemia indicated by anemia, leukopenia and thrombocytopenia (Sittig, 1981).

The following effects have been produced experimentally in laboratory animals, following exposure to benzene: decreased leukocyte and/or erythrocyte counts, reduction in cellular immunity and bone marrow depression (reduced number of granulopoietic stem cells). Animal studies do not indicate that benzene is teratogenic, but the following fetotoxic effects have been found: reduced fetal weight, altered fetal hematopoiesis, fetal skeletal variations and increased

resorptions in pregnant exposed animals. In addition, benzene has produced histopathological changes in ovaries and testes of test animals (ATSDR, 1997).

Benzene and its metabolites have been shown to be mutagenic in a number of in vitro and in vivo studies. Genotoxic effects produced experimentally include structural and numerical chromosome aberrations in humans, animals and cell cultures, and sister chromatid exchanges and micronuclei in vivo animal studies. Benzene exposure has been found to produce an increase in the number of chromosome aberrations associated with myelotoxicity (Sittig, 1981). In addition, sperm head abnormalities, inhibition of DNA and RNA synthesis, DNA binding and interference with cell cycle progression have been shown in vitro studies (ATSDR, 1997). The epidemiologic data indicate that benzene is leukemogenic. The evidence is most convincing for acute myelogenous and acute erythroleukemia, although a correlation has also been found with chronic leukemia. Benzene has been designated a group A human carcinogen (leukemogen) by inhalation. Although data are insufficient to validate the carcinogenicity of benzene via ingestion, it would not be unreasonable that benzene is carcinogenic via this route as well if present in sufficient quantities. The carcinogenicity of benzene via dermal exposure is considered to be lower since benzene is absorbed poorly through the skin (ATSDR, 1997).

Agency for Toxic Substances and Disease Registry (ATSDR) (1997) Toxicological profile for benzene. U.S. Public Health Service.

Sandmeyer, E.E. (1981) *Aromatic hydrocarbons*. In: Patty's Industrial Hygiene and Toxicology, Vol. 2, 3rd ed., Clayton G.D., Clayton F.E., eds. New York. Interscience Publishers. pp. 3253-3283.

Sittig, M. (1981) Handbook of Toxic and Hazardous Chemicals. Noyes Publications.

Bromodichloromethane

Bromodichloromethane is a clear, colorless liquid and one of several trihalomethanes formed when organic subatances in water react with chlorine and bromine (NTP, 1987). Trihalomethanes are widespread in the environment, not only in water supplies but swimming pools, soft drinks, fish samples and disposal sites.

Clinical signs associated with high dose bromodichloromethane administration in mice include sedation, ataxia and enlargement and congestion of the liver and kidneys (NTP, 1987). Microscopic evaluation showed focal inflammation of the liver and intratubular mineralization and epithelial hyperplasia of the kidney. When given to pregnant rats (NTP, 1987), maternal body weight gane was decreased, but no teratogenic effects were observed. A chronic oral reference dose of 0.02 mg/kg-day was developed by EPA based on this reported kidney damage.

Chronic dosing in rats and mice (NTP, 1987) resulted in an increased incidence of hepatic neoplastic nodules in females. Even though bromodichloromethane was not mutagenic in a number of mutagenicity assays (NTP, 1987), EPA has classified it as a group B2 carcinogen. This classification is based on the increased incidence of tumors of the liver, kidney and large intestinesin F344 rats and B6C3F1 mice. EPA has developed an oral cancer slope factor for bromodichloromethane of 0.062 $(mg/kg\text{-}day)^{-1}$.

NTP (National Toxicology Program). 1987. *Toxicology and Carcinogenesis Studies of Bromodichloromethane (CAS No. 75-27-4) in F344/N Rats and B6C3F1 Mice (gavage studies).* NTP TR 321, NIH Publication No. 88-2537, Research Triangle Park, North Carolina.

Carbon Tetrachloride

Humans are sensitive to carbon tetrachloride intoxication by oral, inhalation and dermal routes. Oral and inhalation exposure to high concentrations of carbon tetrachloride results in acute central nervous system effects including dizziness, vertigo, headache, depression, confusion, incoordination and, in severe cases, respiratory failure, coma and death. Gastrointestinal problems including nausea, abdominal pain and diarrhea, often accompany these narcotic effects. Liver and kidney damage can appear after the acute symptoms subside. All symptoms can occur following a single oral or inhalation exposure. Milder narcotic effects followed by liver and kidney damage have been reported following dermal exposure. Although an inhalation exposure of about 1000 ppm for a few minutes to hours will cause the narcotic effects in 100% of the population, large variations in sensitivity are seen. Alcohol intake greatly increases human sensitivity to carbon tetrachloride; consequently, exposure to 250 ppm for 15 minutes can be life threatening to an alcoholic.

Subchronic and chronic exposure to doses as low as 10 ppm can result in liver and kidney damage (ATSDR, 1997). Lung damage has also been reported in animals and humans but is not route specific and is believed to be secondary to kidney damage (Sax and Lewis, 1989). Prolonged exposure has been observed to cause visual effects in both humans and animals. Changes in the visual field, reduced corneal sensitivity, subnormal dark adaption, and changes in color perception have been reported in humans exposed by inhalation to a minimum concentration of 6.4 ppm, 1 hour/day for an average of 7.7 years. Increased hepatic enzyme activities indicative of liver damage have also been observed (ATSDR, 1997).

Maternal toxicity and fetotoxic effects have been reported in rats following oral or inhalation exposure to carbon tetrachloride during gestation (Wilson, 1954; Schwetz et al., 1974). Repeated inhalation exposure of male rats to carbon tetrachloride concentrations of 200 ppm or greater has been reported to cause degeneration of the testicular germinal epithelium as well as severe liver and kidney damage (Adams et al., 1952).

A subchronic reference dose (RfD_s) of 0.007 mg/kg/day has been calculated for oral exposure from a no-observed-adverse-effect level (NOAEL) of 0.71 mg/kg/day determined in a 12-week

rat study. Significantly higher doses caused minimal liver damage (Bruckner et al., 1986). A dose of 7.1 mg/kg/day was considered a lowest-observed-adverse-effect level (LOAEL). A chronic reference dose (RfD_c) of 0.0007 mg/kg/day was calculated by adding an additional uncertainty factor of 10 to account for the use of a subchronic study. Confidence in the oral RfD values is rated medium by EPA.

Although data for the carcinogenicity of carbon tetrachloride in humans are inconclusive, there is ample evidence in animals that the chemical can cause liver cancer. Hepatocellular carcinomas have been induced in hamsters, rats and mice after oral carbon tetrachloride treatment for 16 to 76 weeks. Liver tumors have also been demonstrated in rats following inhalation exposure, but the doses were not quantitatively established. The EPA weight-of-evidence classification for both oral and inhalation exposure is B2, probable human carcinogen based on adequate animal evidence. Carcinogenicity slope factors of 0.13 $(mg/kg/day)^{-1}$ for oral exposure and 0.053 $(mg/kg/day)^{-1}$ for inhalation exposure have been calculated from the oral exposure experiments with hamsters, rats and mice (Della Porta et al., 1961; Edwards et al., 1942; NCI, 1976a, 1976b; Weisburger, 1977). A drinking water unit risk of 3.7×10^{-6} $(\mu g/L)^{-1}$ and an inhalation unit risk of 1.5×10^{-5} $(\mu g/m^3)^{-1}$ have also been calculated by USEPA.

Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 6: 50-66.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Carbon Tetrachloride. Prepared by Life Systems, Inc. for: Agency for Toxic Substances and Disease Registry, U.S. Public Health Service in collaboration with U. S. Environmental Protection Agency.

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, U. Luthra, G.M. Kyle and D. Aconta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

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NCI (National Cancer Institute). 1976b. Report on Carcinogenesis Bioassay of Trichloroethylene. National Cancer Institute Carcinogenesis Technical Report Series, No. 2. NCI-CG-TR-2.

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Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1974. Embryo and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28: 452-464.

Weisburger, E.K. 1977. Carcinogenicity studies on halogenated hydrocarbons. Environ. Health Perspect. 21: 7-16.

Wilson, J.T. 1954. Influence of the offspring of altered physiologic states during pregnancy in the rat. Ann. NY Acad. Sci. 57: 517-525.

Chlorobenzene

The chemical formula for chlorobenzene is C_6H_5Cl, and its molecular weight is 112.56 g/mol. Chlorobenzene occurs as a colorless flammable liquid, with low solubility in water. Chlorobenzene has an aromatic, almond-like odor, with an odor threshold of 1 to 8 mg/m^3. The vapor pressure for chlorobenzene is 8.8 mm Hg at 20 EC, and its log octanol/water partition coefficient (log K_{ow}) is 2.84. The primary uses of chlorobenzene are as a solvent for pesticide formulations, diisocyanate manufacture, and degreasing automobile parts and for the production of nitrochlorobenzene. In the past, chlorobenzene was used as an intermediate in phenol and DDT production (ATSDR, 1997).

Human exposure to chlorobenzene appears to be primarily occupational. In urban areas, chlorobenzene may be released to the ambient air during its manufacture and use. Chlorobenzene or its breakdown products can be detected in urine, exhaled breath, blood, and body fat to determine whether or not exposure has occurred. A child who ingested chlorobenzene became unconscious and cyanotic and had muscle spasms but recovered completely (ATSDR, 1997) Acute (short-term) inhalation exposure of cats to chlorobenzene produced narcosis, restlessness, tremors, and muscle spasms (HSDB, 1993). Acute animal tests, such as the LC_{50} and LD_{50} tests in rats, mice, rabbits, and guinea pigs, have demonstrated chlorobenzene to have low acute toxicity by inhalation and moderate acute toxicity from oral exposure (RTECS, 1993).

Chronic (long-term) exposure of humans to chlorobenzene affects the CNS. Signs of neurotoxicity include numbness, cyanosis, hyperesthesia (increased sensation), and muscle spasms. Headaches and irritation of the mucosa of the upper respiratory tract and eyes have also been reported in humans chronically exposed via inhalation (USEPA, 1989). The CNS,

liver, and kidneys have been affected in animals chronically exposed to chlorobenzene by inhalation (ATSDR, 1997). Chronic ingestion of chlorobenzene has resulted in damage to the kidneys and liver in animals (USEPA, 1989).

The RfD for chlorobenzene is 0.02 mg/kg/d based on histopathologic changes in the liver in dogs. EPA has medium confidence in the study on which the RfD was based because it provided both a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL) and incorporated several biochemical and biological endpoints; medium confidence in the database because several subchronic, chronic, developmental, and reproductive toxicity studies provide supportive data, but they did not give a complete assessment of toxicity; and, consequently, medium confidence in the RfD.

No information is available on the reproductive or developmental effects of chlorobenzene in humans. Chronic inhalation exposure of rats to chlorobenzene did not adversely affect reproductive performance or fertility. However, a slight increase in the incidence of degenerative testicular changes was observed. Chlorobenzene does not appear to be a developmental toxicant and did not produce structural malformations in rats and rabbits acutely exposed via inhalation (USEPA, 1989).

No information is available on the carcinogenic effects of chlorobenzene in humans.In a study of rats and mice exposed to chlorobenzene via gavage (experimentally placing the chemical in the stomach), an increased incidence of neoplastic nodules of the liver in male rats was observed but not in mice or female rats (ATSDR, 1997). EPA has classified chlorobenzene as a Group D, not classifiable as to human carcinogenicity.

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U.S. Department of Health and Human Services. Hazardous Substances Data Bank (HSDB, online database). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.

U.S. Department of Health and Human Services. Registry of Toxic Effects of Chemical Substances (RTECS, online database). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.

U.S. Environmental Protection Agency (USEPA). *Updated Health Effects Assessment for Chlorobenzene*. EPA/600/8-89/099. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH. 1989.

Chloroform

Chloroform is a colorless, volatile liquid that is widely used as a general solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (Torkelson and Rowe, 1976; IARC, 1976). Chloroform is rapidly absorbed from the lungs and the gastrointestinal tract, and to some extent through the skin. It is extensively metabolized in the body, with carbon dioxide as the major end product. The primary sites of metabolism are the liver and kidneys. Excretion of chloroform occurs primarily via the lungs, either as unchanged chloroform or as carbon dioxide (ATSDR, 1997).

Target organs for chloroform toxicity are the liver, kidneys, and central nervous system. Liver effects (hepatomegaly, fatty liver, and hepatitis) were observed in individuals occupationally exposed to chloroform (Bomski et al., 1967). Several subchronic and chronic studies by the oral or inhalation routes of exposure documented hepatotoxic effects in rats, mice, and dogs (Palmer et al., 1979; Munson et al., 1979; Heywood et al., 1979). Renal effects were reported in rats and mice following oral and inhalation exposures (Roe et al., 1979; Reuber, 1976; Torkelson et al., 1976), but evidence for chloroform-induced renal toxicity in humans is sparse. Chloroform is a central nervous system depressant, inducing narcosis and anesthesia at high concentrations. Lower concentrations may cause irritability, lassitude, depression, gastrointestinal symptoms, and frequent and burning urination (ATSDR, 1997).

Developmental toxicity studies with rodents indicate that inhaled and orally administered chloroform is toxic to dams and fetuses. Possible teratogenic effects were reported in rats and mice exposed to chloroform by inhalation (Schwetz et al.; 1974; Murray et al., 1979). Chloroform may cause sperm abnormalities in mice and gonadal atrophy in rats (Palmer et al, 1979; Reuber, 1979; Land et al., 1981).

A Reference Dose (RfD) of 0.01 mg/kg/day for subchronic and chronic oral exposure was calculated from a lowest-observed-adverse-effect level (LOAEL) of 15 mg/kg/day based on fatty cyst formation in the liver of dogs exposed to chloroform for 7.5 years (Heywood et al., 1979).

Epidemiological studies indicate a possible relationship between exposure to chloroform present in chlorinated drinking water and cancer of the bladder, large intestine, and rectum. Chloroform is one of several contaminants present in drinking water, but it has not been identified as the sole or primary cause of the excess cancer rate (ATSDR, 1997; U.S. EPA, 1985). In animal carcinogenicity studies, positive results included increased incidences of renal epithelial tumors in male rats, hepatocellular carcinomas in male and female mice, and kidney tumors in male mice (Jorgensen et al., 1985; Roe et al., 1979; NCI, 1976).

Based on U.S. EPA guidelines, chloroform was assigned to weight-of-evidence Group B2, probable human carcinogen, on the basis of an increased incidence of several tumor types in rats and in three strains of mice. The carcinogen slope factor (q_1^*) for chloroform is 6.1E-3 $(mg/kg/day)^{-1}$ for oral exposure and 8.1E-2 $(\mu g/m^3)^{-1}$ for inhalation exposure. An inhalation

unit risk of 2.3E-5 $(\mu g/m^3)^{-1}$ is based on hepatocellular carcinomas in mice in an oral gavage study.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Chloroform. Prepared by Syracuse Research Corporation, under Contract 68-C8-0004. U.S. Public Health Service. ATSDR/TP-88/09.

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NCI (National Cancer Institute). 1976. Report on Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Washington, DC. NTIS PB 264018.

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Schwetz, B.A., B.K.L. Leong and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled chloroform in rats. Toxicol. Appl. Pharmacol. 28: 442-451.

Torkelson, T.R. and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons containing chlorine, bromine and iodine. In: G.D. Clayton and E. Clayton, Eds. Patty's Industrial Hygiene and Toxicology, Vol. 2B. John Wiley & Sons, New York, pp. 3462-3469.

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U.S. EPA. 1985. Health Assessment Document for Chloroform. Final Report. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-84/004F, NTIS PB86-105004/XAB.

Dichlorobenzenes

1,4-Dichlorobenzene, also referred to as para-DCB, p-DCB, paracide, Paramoth®, Parazene®, PDB, and Santochlor®, has a benzene ring with two chlorine atoms attached at the 1 and 4 carbon atoms; it does not occur naturally (ATSDR, 1997). Two additional isomers, 1,3-dichlorobenzene and 1,2-dichlorobenzene, also exist. 1,4-Dichlorobenzene is used to make mothballs, deodorant blocks used in restrooms, and in animal holding facilities to control odors (ATSDR, 1997). It also has applications in fumigants, insecticides, lacquers, paints, and seed disinfection products (Leber and Benya, 1994). Of the 1300 sites on the United States Environmental Protection Agency's National Priorities List, dichlorobenzenes have been identified on at least 244 sites. Drinking water samples from U.S. surface water sources, environmental hazardous waste sites, and food have been reported to contain dichlorobenzenes (ATSDR, 1997).

Detectable concentrations of dichlorobenzenes were found in adipose tissue and blood samples taken from Tokyo residents (Morita and Ohi, 1975; Morita et al., 1975). A national survey of various volatile organic chemicals demonstrated dichlorobenzenes in the three adipose tissues sampled. In addition, studies have shown that babies can receive dichlorobenzenes from mother's milk (ATSDR, 1997). Dichlorobenzenes are absorbed by experimental animals via inhalation, gavage, or subcutaneous injection (Hawkins et al., 1980). Data from oral administration of 1,4-dichlorobenzene to rabbits indicated oxidation to 2,5-dichlorophenol, which was found in the urine as a conjugate of glucuronic and sulfuric acids (Azouz et al., 1955). Other metabolites identified in the blood and urine of rats were 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone.

Severe hypochromic, microcytic anemia with excessive polychromasia, marginal nuclear hypersegmentation of the neutrophils, and a small number of red blood cells with Heinz bodies developed in a pregnant woman (21 years old) who consumed 1–2 blocks of 1,4-dichlorobenzene toilet air freshener per week throughout her pregnancy (Campbell and Davidson, 1970). A 19-year-old female who consumed 4–5 moth pellets containing 1,4-dichlorobenzene on a daily basis for 2.5 years developed symmetrical, well-demarcated areas of increased pigmentation over various parts of her body, which disappeared over a 4-month period after discontinuing the ingestion (Frank and Cohen, 1961).

In rats, 13-week gavage studies resulted in decreased hematocrit levels, red blood cell counts, and hemoglobin concentrations at 300 mg/kg/day (NTP, 1987). Oral administration of 1200 and 1500 mg/kg/day resulted in degeneration and necrosis of rat hepatocytes. Increased incidences of hepatocellular degeneration and individual cell necrosis were observed in male and female mice gavaged with 600–1800 mg/kg/day.

Rats exposed via inhalation to 96–341 ppm of 1,4-dichlorobenzene intermittently for 5–7 months had cloudy swelling and degeneration of hepatic parenchymal cells in the central zone of the liver. Increased liver weights in the male and/or female rats occurred above 96 ppm (Hollingsworth et al., 1956). During a 2-generation study, adult rats exposed to 538 ppm exhibited tremors, ataxia, and hyperactivity; decreased grooming behavior; and an unkempt appearance (Tyl and Neeper-Bradley, 1989). Both generations of offspring in the 538 ppm group had lower body weights at lactation day 4, and average litter size and survival were decreased. Selected animals from the first filial generation still had reduced body weights at 5 weeks post-exposure.

No epidemiologic studies or case reports addressing the carcinogenicity of 1,4-dichlorobenzene in humans were available. In a 2-year study, female rats and male and female mice were gavaged with 300 and 600 mg/kg/day and male rats were gavaged with 150 and 300 mg/kg/day (NTP, 1987). Nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of the renal tubular epithelium were noted in male rats receiving 150 and 300 mg/kg/day. Female rats gavaged with 300 and 600 mg/kg/day had an increased incidence of nephropathy and minimal hyperplasia of the renal pelvis or tubules. The following tumors were described as being present in the animals: renal tubular adenocarcinomas in male rats (controls, 2%; low dose, 6%; high dose, 14%), a marginal increase in mononuclear cell leukemia in male rats (control, 10%; low dose, 14%; high dose, 22%), hepatocellular carcinomas in male mice (controls, 28%; low dose, 22.5%; high dose, 64%) and in female mice (controls, 10%; low dose, 10.4%; high dose, 38%), and hepatocellular adenomas in male mice (controls, 10%; low dose, 26.2%; high dose, 32%) and in female mice (controls, 20%; low dose, 12.5%; high dose, 42%). In this NTP study, the tumor incidence in female controls was higher than the historical control. In both male and female mice, hepatocellular degeneration with resultant initiation of tissue repair was present. These findings resulted in a speculation by NTP (1987) that 1,4-dichlorobenzene was acting as a tumor promotor for liver tumors in male and female mice.

Reference concentrations (RfC) of 2.5 mg/m^3 (0.42 ppm) for subchronic inhalation exposure (EPA 1995b) and 0.8 mg/m^3 (0.13 ppm) for chronic inhalation exposure for 1,4-dichlorobenzene were derived based on increased liver weights in the P1 males exposed via inhalation to 1,4-dichlorobenzene from the study of Tyl and Neeper-Bradley (1989). The No Observed Adverse Effects Level (NOAEL) was 301 mg/m^3 (50 ppm). The Lowest Observed Adverse Effects Level (LOAEL) was 902 mg/m^3 (150 ppm). 1,4-Dichlorobenzene has been classified as C, possible carcinogen to humans. For oral exposure, the slope factor was 0.024 (mg/kg/day)$^{-1}$, and the unit risk was 6.8E-7 (μg/L)$^{-1}$.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for 1,4-Dichlorobenzene., ATSDR/TP-92/10, prepared by Life Sciences, Inc., under Subcontract to Clement Associates, Inc., Contract No. 205-88-0608.

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NTP (National Toxicology Program). 1987. *Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene (CAS No. 106-46-7) in F344/N Rats and B6C3F1 Mice (gavage studies)*. NTP TR 319, NIH Publication No. 87-2575, Research Triangle Park, North Carolina.

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1,2-Dichloroethane

1,2-Dichloroethane (1,2-DCA or ethylene dichloride) is a clear, colorless, volatile liquid with a pleasant odor. Approximately 80% of 1,2-dichloroethane is used to produce vinyl chloride. It is also used to produce vinylidene chloride, 1,1,1- trichloroethane, TCE, PCE, aziridines and ethylene diamines. Minor applications include various solvent functions, use as a fumigant for grains, upholstery and carpets and as a lead-scavenging agent in gasoline (IRP, 1985).

1,2-DCA is readily absorbed through the lungs following inhalation exposure in both humans and animals (ATSDR, 1997). Absorption from the gastrointestinal tract is rapid and complete. Excretion of unmetabolized 1,2-DCA is almost exclusively via the lungs. However, metabolism and excretion of metabolites by other routes is extensive and dose related. Tissue distribution of 1,2-DCA is consistent with its lipophilic nature. It crosses the blood-brain and placental barriers and distributes into breast milk (U.S. EPA, 1985).

Short-term ingestion or inhalation of 1,2-DCA results in symptoms of CNS depression, gastrointestinal upset and systemic injury to the liver, kidneys and lungs (Clayton and Clayton, 1981). Long term exposure of workers to 1,2-DCA in an occupational environmment have been associated with loss of appetite, nausea, vomiting, epigastric pain, irritation of the mucous membrane, neurologic changes and liver and kidney impairment (IRP, 1985).

Acute inhalation exposure of a number of animal species to 1,2-DCA resulted in death in rats and guinea pigs at 400 ppm and in mice, rabbits and dogs at 1500 ppm (Heppel et al., 1945, 1946; Spencer et al., 1951). Liver and kidney effects were noted, as well as associated adverse effects to the respiratory and cardiovascular systems. A 15 percent increase in fat accumulation and an increase in liver triglycerides were observed in rats fed 80 mg/kg/day in the diet for 5 to 7 weeks (Alumot et al., 1976). No changes in liver weight was reported at this dose level. No hepatic effects were noted in the same study at 30 mg/kg/day. No hepatotoxicity was noted in mice administered up to 189 mg/kg/day in drinking water for 90 days (Munson et al., 1982). Chronic exposure of rats to 25 mg/kg/day in food for two years did not result in abnormalities in liver function as measured by transaminases and cholesterol values (Alumot et al., 1976). No dose-related reproductive effects were seen in mice fed 5-50 mg/kg/day in drinking water (Lane et al., 1982) or rats fed diets containing 12.5 or 25

mg/kg/day (Alumot et al., 1976). Intermittent exposure (7 hr/day) of female rats to 4.69 +/- 7 ppm of 1,2-DCA for 4 months prior to the mating period followed by inhalation exposure during pregnancy resulted in a statistically significant increase in embryo mortality (Vozavaya, 1977).

In-vivo exposure of mice to 1000 ppm of 1,2-DCA vapors for 4 hours or to a single nontoxic oral dose of 100 mg/kg resulted in irreversible DNA damage as revealed by single-stranded breaks in the hepatocytes of mice (Storer et al., 1984). 1,2-DCA has been found to be carcinogenic in rats and mice following oral gavage exposure (NCI, 1978). A dose of 47 mg/kg/day administered to rats produced tumors at locations remote from the site of administration. Statistically significant increases in multiple tumor types (malignant and nonmalignant) were noted in treated animals of both species. An increased incidence of fibromas of the subcutaneous tissue and hemangiosarcomas of the spleen, liver, pancreas and adrenal gland was observed in male rats exposed to 47 or 95 mg/kg/day. Male rats exposed to 95 mg/kg/day were observed to have an increase in squamous-cell carcinomas of the forestomach, and female rats at this dosage had increased adenocarcinomans and fibroadenomas of the mammary gland.

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Methyl tert-butyl ether

The chemical formula for methyl *tert*-butyl ether is $C_5H_{12}O$, and its molecular weight is 88.15 g/mol. Methyl *tert*-butyl ether occurs as a colorless liquid, with a vapor pressure of 245 mm Hg at 25 EC. Methyl *tert*-butyl ether is used as an octane booster in unleaded gasoline. It is also used in the manufacture of isobutene (HSDB, 1993; Merck, 1989).

The general population may be exposed to methyl *tert*-butyl ether via the inhalation of air contaminated from its use as an octane booster or a pollution reducer in unleaded gasoline or by dermal contact. Workers may be occupationally exposed via inhalation or dermal contact. Acute (short-term) exposure of humans to methyl *tert*-butyl ether has occurred via injection into the gallbladder during its use as a medical treatment to dissolve cholesterol gallstones. Nausea, vomiting, and sleepiness have been observed; in one case renal failure was reported (HSDB, 1993). Acute inhalation exposure has resulted in ataxia and abnormal gait in rats. Acute animal tests, such as the LC_{50} and LD_{50} test in rats, have demonstrated methyl *tert*-butyl ether to have low acute toxicity via inhalation and moderate acute toxicity via ingestion (RTECS, 1993).

No information is available on the chronic (long-term) health effects of methyl *tert*-butyl ether in humans. Increased liver and kidney weights, decreased brain weight, swollen periocular tissue, and ataxia have been reported in rats following chronic inhalation exposure. Increased severity of spontaneous renal lesions and increased prostration (lying flat or exhaustion) were reported in females only. Increased liver, kidney, spleen, and adrenal weights; ataxia; and decreased brain weight, body weight, and body weight gain have been observed in mice chronically exposed to methyl *tert*-butyl ether by inhalation. Increased prostration was reported in females (HSDB, 1993).

The RfC for methyl *tert*-butyl ether is 3.0 mg/m^3 based on increased liver and kidney weights, increased prostration in females, and swollen periocular tissues in male and female rats. EPA has medium confidence in the study on which the RfC was based because it was well designed (e.g., with respect to exposure protocol, number of animals, and exposure duration), identified a consistent lowest-observed-adverse-effect level (LOAEL) and no-observed-adverse-effect level (NOAEL) for a number of organ systems, and involved extensive histopathology on both sexes.

However, the results of the rat study are confounded by the high mortality in the males, which is presumed to be the result of rat chronic nephropathy. EPA has medium to high confidence in the database because of the existence of chronic and subchronic bioassays in more than one species, developmental studies in several different species, and the existence of single- and two-generation reproductive studies in the rat; and, consequently, medium to high confidence in the RfC.

No information is available on the reproductive or developmental effects of methyl *tert*-butyl ether in humans. In rats exposed via inhalation, reduced body weight and body weight gain in pups and decreased pup viability have been reported. A decreased number of viable implantations, increased maternal toxicity, dead fetuses, and late resorptions; and skeletal variations have been reported in mice exposed via inhalation (HSDB, 1993).

No information is available on the carcinogenic effects of methyl *tert*-butyl ether in humans or animals. EPA has not classified methyl *tert*-butyl ether with respect to potential carcinogenicity.

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Methylene Chloride

Methylene chloride (CH_2Cl_2), also known as dichloromethane is a colorless volatile liquid with a penetrating ether-like odor. In industry, methylene chloride is widely used as a solvent in paint removers, degreasing agents, and aerosol propellants; as a polyurethane foam-blowing agent; and as a process solvent in the pharmaceutical industry. The compound is also used as an extraction solvent for spice oleoresins, hops, and caffeine (ATSDR, 1997; IARC, 1986).

Methylene chloride is readily absorbed from the lungs, the gastrointestinal tract, and to some extent through the skin. Metabolism of methylene chloride produces CO_2 and CO, which readily binds with blood hemoglobin to form carboxyhemoglobin (CO-Hb). The primary adverse health effects associated with methylene chloride exposure are central nervous system (CNS) depression and mild liver effects. Neurological symptoms described in individuals occupationally exposed to methylene chloride included headaches, dizziness, nausea, memory loss, paresthesia, tingling hands and feet, and loss of consciousness (Welch, 1987). Major effects following acute inhalation exposure include fatigue, irritability, analgesia, narcosis, and death (ATSDR, 1997). CNS effects have also been demonstrated in animals following acute exposure to methylene chloride (Weinstein et al., 1972; Berger and Fodor, 1968).

Impaired liver function has been associated with occupational exposure to methylene chloride (Welch, 1987). Liver effects have also been documented in a number of inhalation studies with laboratory animals. Subchronic exposure of rats, mice, dogs, and monkeys caused mild hepatic effects such as cytoplasmic vacuolization and fatty changes (USEPA, 1983; Haun et al., 1972; Weinstein and Diamond, 1972; Heppel, 1944). Hepatocellular foci, fatty changes, and necrosis were reported following chronic inhalation exposure of rats and mice (Nitschke et al., 1986a; NTP, 1986). Chronic oral exposure to methylene chloride via drinking water resulted in histopathological alterations of the liver in rats and mice (NCA, 1982, 1983). In addition, inhalation exposure of rats caused nonspecific degenerative and regenerative changes in the kidneys (USEPA, 1983; Haun et al., 1972).

A subchronic and chronic oral reference dose (RfD) of 6E-2 mg/kg/day for methylene chloride has been calculated by USEPA. This value is based on a NOAEL of 5.85 mg/kg/day derived from a chronic drinking water study with rats (NCA, 1982). This same study was adapted for the derivation of the subchronic and chronic reference concentration (RfC) of 3E+0 mg/m^3 (NOAEL, 694.8 mg/m^3).

Studies of workers exposed to methylene chloride have not recorded a significant increase in cancer cases above the number of cases expected for nonexposed workers (Hearne et al., 1987; Ott et al., 1983a; Friedlander et al., 1978). However, long-term inhalation studies with rats and mice demonstrated that methylene chloride causes cancer in laboratory animals. Mice exposed via inhalation to high concentrations of methylene chloride (2000 or 4000 ppm) exhibited a significant increase of malignant liver and lung tumors compared with nonexposed controls (NTP, 1986). Rats of both sexes exposed to concentrations of methylene chloride ranging from 500 to 4000 ppm showed increases of benign mammary tumors (Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984). An inhalation study with rats and hamsters revealed sarcomas of the salivary gland in male rats, but not in female rats or hamsters (Burek et al., 1984). Liver tumors observed in rats and mice that ingested methylene chloride in drinking water for 2 years provided suggestive evidence of carcinogenicity (NCA, 1982, 1983). Based on inadequate evidence of carcinogenicity in humans and on sufficient evidence in animals, USEPA has placed methylene chloride in weight-of-evidence group B2, probable human carcinogen. A slope factor and unit risk of 7.5E-3 $(mg/kg/day)^{-1}$ and 2.1E-7 $(ug/L)^{-1}$, respectively, was derived for oral exposure to methylene chloride. The inhalation unit risk is 4.7E-7 $(ug/m^3)^{-1}$.

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Tetrachloroethene

Tetrachloroethene (PCE) is readily absorbed following inhalation and oral exposure (ATSDR, 1997). Tetrachloroethene vapors and liquid also can be absorbed through the skin (USEPA, 1985a,b). Humans acutely exposed to tetrachloroethene at levels as low as 216 mg/m^3 experienced respiratory irritation, dizziness, and sleepiness (Rowe et al., 1952). The principal toxic effects of tetrachloro-ethene in humans and animals following acute and longer-term exposures in-clude CNS depression and fatty infiltration of the liver and kidney with concomitant changes in serum enzyme activity levels indicative of tissue damage (U.S. EPA, 1985a,b; Buben and O'Flaherty, 1985). Mice subchronically exposed to tetrachloroethene did not show any adverse liver effects at 20 mg/kg/day (Buben and O'Flaherty, 1985). Humans exposed to doses of between 136 and 1,018 mg/m^3 for 5 weeks develop CNS effects, such as lassitude and signs of inebriation (Stewart et al. 1974). The offspring of female rats and mice exposed to high concentrations of tetrachloroethene (300 mg/m^3) for 7 hours daily on days 6 to 15 of gestation developed toxic effects, including a decrease in fetal body weight in mice and a small but significant increase in fetal resorption in rats (Schwetz, Leong, and Gehring, 1975). Mice also exhibited develop-men-tal effects, including subcutaneous edema and delayed ossification of skull bones and sternebrae (Schwetz, Leong, and Gehring, 1975). In an NCI (1977) bioassay, increased incidence of hepatocellular carcinoma were observed in both sexes of B6C3F1 mice administered tetrachloroethylene (386–1,072 mg/kg/day) in corn oil by gavage for 78 weeks. Increased incidence of mononuclear cell leukemia and renal adenomas and carcinomas (combined) have also been observed in long-term bioassays in which rats were exposed to tetrachloroethene by inhalation at air concentrations of 200–400 mg/m^3 (NTP, 1986).

Tetrachloroethene is currently under review by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and estimates of cancer potency were recently withdrawn by USEPA (1995). However, the USEPA National Center for Environmental Assessment (USEPA, 1998) currently classifies tetrachloroethene as a Group B2/C carcinogen (Probable/Possible Human Carcinogen). USEPA (1996a) has reported an oral slope factor of 5.2×10^{-2} $(mg/kg/day)^{-1}$ based on liver tumors observed in the NCI (1977) gavage bioassay for mice. The cancer slope factor is currently under review by USEPA. USEPA (2001) has also derived an oral RfD of 1×10^{-2} mg/kg/day for tetrachloroethene based on a 6-week gavage study by Buben and O'Flaherty (1985). In this study, liver weight/body weight ratios were significantly increased in mice and rats treated with 71 mg/kg/day tetrachloroethene but not in animals treated with 14 mg/kg/day.

Using a NOAEL of 14 mg/kg/day and applying an uncertainty factor of 1,000 the RfD was derived.

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Trichloroethene

Absorption of trichloroethene (TCE) from the gastrointestinal tract is virtually complete. Absorption following inhalation exposure is proportional to concentration and duration of exposure (USEPA, 1985). TCE is a CNS depressant following acute and chronic exposures. In humans, single oral doses of 15–25 mL (21–35 grams) have resulted in vomiting and abdominal pain, followed by transient unconsciousness (Stephens, 1945). High-level exposure can result in death due to respiratory and cardiac failure (ATSDR, 1995). Hepatotoxicity has been reported in human and animal studies following acute exposure to TCE (ATSDR, 1997). Nephrotoxicity has been observed in animals following acute exposure to TCE vapors (ACGIH, 1986; Torkelson and Rowe, 1981). Subacute inhalation exposures in mice have resulted in transient increased liver weights (Kjellstrand *et al.*, 1983a,b). Industrial use of TCE is often associated with adverse dermatological effects including reddening and skin burns on contact with the liquid form, and dermatitis resulting from vapors. These effects are usually the result of contact with concentrated solvent. However, no effects have been reported following exposure to TCE in dilute, aqueous solutions (USEPA, 1985). TCE has caused significant increases in the incidence of hepatocellular carcinomas in mice (NCI, 1976), renal tubular-cell neoplasms in rats exposed by gavage (NTP, 1983), and pulmonary adenocarcinomas in mice following inhalation exposure (Fukuda *et al.*, 1983; Maltoni *et al.*, 1986). TCE was mutagenic in *Salmonella typhimurium* and in *E. coli* (strain K-12), utilizing liver microsomes for activation (Greim *et al.*, 1977).

USEPA is currently reviewing the carcinogenicity of TCE. The National Center for Environmental Assessment (NCEA) currently classifies TCE as a Group B2/C (Probable/Possible Human Carcinogen) based on inadequate evidence in humans and sufficient evidence of carcinogenicity from animal studies. NCEA (USEPA, 1998) reports a provisional oral cancer slope factor of 1.1×10^{-2} $(mg/kg\text{-}day)^{-1}$ based on two gavage studies conducted in mice in which an increased incidence of liver tumors were observed (Maltoni *et al.*, 1986; Fukuda *et al.*, 1983). The cancer estimate is currently under review by USEPA.

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Xylenes

Xylenes are colorless liquid organic molecules with a sweet odor and a high degree of lipid solubility. There are three isomers of xylene: meta- ortho- and para-xylene (m-, o- and p-xylene, respectively). The term "total xylenes" is used to designate a mixture of the three possible isomers, in any proportions. They are commonly used as industrial solvents, as components of paints, varnishes, cleaners, degreasers and gasoline and as chemical intermediates in the manufacture of other chemicals, plastics and synthetic fibers. Xylenes are volatile molecules and

therefore, evaporate quickly. They are also flammable and may pose a fire hazard if handled improperly (ATSDR, 1997).

Xylenes are readily absorbed by all routes of exposure. Xylenes are very soluble in blood and therefore are absorbed easily into the systemic circulation during exposure (Astrand, 1982). Following absorption, distribution occurs rapidly to all organs, including fetal tissue, with greatest distribution occurring to organs having a high lipid content, such as adipose tissue, bone marrow and brain (Astrand, 1982; Engstron and Bjurstrom, 1978; Riihimaki et al., 1979). In humans, xylenes are primarily metabolized by the mixed function oxidase enzyme system to methylbenzyl alcohols which are further oxidized by alcohol and aldehyde dehydrogenase to yield methyl benzoic acids. The acids are readily conjugated and excreted in urine (Fishbein, 1985). In addition, a small percentage (3-6%) is exhaled unchanged due to the volatile nature of these compounds.

Human data suggests that the three xylene isomers all produce qualitatively similar effects, although the individual isomers are not necessarily equal in potency with regard to a given effect (ATSDR, 1997). Exposure, by any route, results in primarily central nervous system effects that may include headaches, nausea, mental confusion, narcosis, impaired learning and memory, dizziness, tremors, unconsciousness and coma, depending on dose and length of exposure. High doses may result in death. The respiratory system may also be a target of xylene toxicity in humans, producing respiratory tract irritation, pulmonary edema and inflammation after inhalation. Ocular irritation may result following exposure to xylene vapors. Skin irritation, dryness and scaling may result following dermal exposure. Limited data are available concerning effects of exposure on the hepatic, renal, cardiovascular, musculoskeletal or hematological system. Insufficient information is available regarding the developmental and reproductive toxicity of xylenes in humans.

Exposure to xylenes produces similar effects in humans and laboratory animals. The central nervous system is the primary target for both short-term and long-term exposures. Respiratory effects are observed following inhalation exposure. Data from animal studies provide limited evidence that xylene may produce cardiovascular effects (arrhythmias, atrial fibrillation and alterations in blood vessels and blood flow) (Morvai et al., 1976, 1987), hepatic effects (enzyme induction, increased liver weight, ultrastructural alterations) (Condie et al., 1988; Elovaara et al., 1980; Elovaara, 1982) and renal effects (enzyme induction, renal atrophy, tubular alterations) (Condie et al., 1988; Elovaara, 1982; Toftgard and Nilsen, 1982). These results suggest that humans might be at increased risk of developing such effects following exposure. Findings in animal studies suggest that xylenes may produce developmental defects including increased fetal death, decreased fetal weight, delayed skeletal development and gross anomalies (Marks et al., 1982; Ungvary et al., 1980). No animal data exists suggesting effects on reproductive organs, the musculoskeletal system or hematological system.

Xylenes have been tested for genotoxicity in a variety of in vitro and in vivo assays. Results of the various assays indicate that xylenes are nongenotoxic following in vitro and in vivo exposure (ATSDR, 1997). No evidence of carcinogenicity exists in humans or laboratory animals (ATSDR, 1997).

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SEMIVOLATILE ORGANICS

Acetophenone

The chemical formula for acetophenone is C_8H_8O, and its molecular weight is 120.15 g/mol. Acetophenone occurs as a colorless liquid that is slightly soluble in water (USEPA, 1987; HSDB, 1993; Merck, 1989). Acetophenone has a sweet pungent odor of orange blossom or jasmine, with an odor threshold of about 0.83 mg/m^3. The vapor pressure for acetophenone is 0.372 mm Hg at 25 EC, and its log octanol/water partition coefficient (log K_{ow}) is 1.58 (USEPA, 1987). Acetophenone is used in perfumery as a fragrance ingredient in soaps, detergents, creams, lotions, and perfumes; as a flavoring agent in foods, nonalcoholic beverages, and tobacco; as a specialty solvent for plastics and resins; as a catalyst for the polymerization of olefins; and in organic syntheses as a photosensitizer (USEPA, 1987; HSDB, 1993; Merck, 1989).

Occupational exposure to acetophenone may occur during its manufacture and use (Sittig, 1985). Acetophenone has been detected in ambient air and drinking water; exposure of the general public may occur through the inhalation of contaminated air or the consumption of contaminated water (USEPA, 1987). Hippuric acid may be monitored in the urine to determine whether or not exposure to acetophenone has occurred (Sittig, 1985).

Acute (short-term) exposure of humans to acetophenone vapor may produce skin irritation and transient corneal injury. One study noted a decrease in light sensitivity in exposed humans (USEPA, 1987; HSDB, 1993). Acute oral exposure has been observed to cause hypnotic or sedative effects, hematological effects, and a weakened pulse in humans (Sittig, 1985; HSDB, 1993). Congestion of the lungs, kidneys, and liver were reported in rats acutely exposed to high levels of acetophenone via inhalation (HSDB, 1993). Tests involving acute exposure of animals, such as the LD_{50} test in rats, mice, and rabbits, have demonstrated acetophenone to have moderate acute toxicity from oral or dermal exposure (RTECS, 1993).

No information is available on the chronic (long-term) effects of acetophenone in humans. Degeneration of olfactory bulb cells was reported in rats chronically exposed via inhalation. In another study, chronic inhalation exposure of rats produced hematological effects and, at high doses, congestion of cardiac vessels and pronounced dystrophy of the liver (USEPA, 1987; HSDB, 1993). In two studies, no effects were observed in rats chronically exposed to acetophenone in their diet (USEPA, 1987; HSDB, 1993).

The RfD for acetophenone is 0.1 mg/kg/d based on general toxicity in rats. EPA has low confidence in the study on which the RfD was based because, although the animals were tested by a relevant route of administration at three levels in a subchronic study and several endpoints were monitored, the sample size was inadequate and the range of doses tested did not define a lowest-observed-adverse-effect level (LOAEL); low confidence in the database because, although no-observed-adverse-effect levels (NOAELs) were defined, supporting studies could not be located in the available literature; and, consequently, low confidence in the RfD.

No information is available on the reproductive or developmental effects of acetophenone in humans.In one study of pregnant rats exposed dermally, no effects on reproduction or development were noted (USEPA, 1987; HSDB, 1993).

No information is available on the carcinogenic effects of acetophenone in humans or animals.EPA has classified acetophenone as a Group D, not classifiable as to human carcinogenicity.

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Atrazine

Atrazine (2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine), is a chlorinated triazine herbicide used to control certain weeds in corn, sorghum, sugarcane, pineapple, macadamia nuts, and citrus fruits. It is also used for general weed control on industrial and nonagricultural land.[1]

Herbicides with atrazine as the active ingredient have been sold under trade names of Atrazine, AAtrex, Atratol, Gesaprim, and Zeaphos.[2] Atrazine is also a component of other herbicides such as Alazine,[3] Bicep,[2] Bullet, Extrazine, Prozine, Rastra,[3] Stuazine,[2] and Tomahawk.[3] Manufacturers of atrazine include Ciba-Geigy Corp., E.I. du Pont de Nemours & Co. Inc., Drexel Chemical Co., Oxon Italia, and Industria Prodotti Chimici.[2]

Atrazine has been widely used in the United States since 1958. The most recent market estimates from the U.S. Environmental Protection Agency (EPA) show that more atrazine (70 to 90 million pounds of active ingredient annually) is used than any other U.S. pesticide, excluding wood preservatives. [4]

According to the National Institute for Occupational Safety and Health, atrazine is a mild skin irritant and a severe eye irritant. The oral LD_{50}, the dose that will kill 50 percent of a population of test animals, is 672 milligrams per kilogram of body weight (mg/kg) in rats.[8] If the human LD_{50} is similar, less than two ounces would be a toxic dose for a typical (70 kilogram) adult male.

Chronic toxicity tests of technical grade atrazine have demonstrated diminished weight gain, increased irritability, and probable anemia in rats. (The No Observable Effect Level (NOEL) for these effects was 70 parts per million (ppm). NOELs are used by EPA and other regulatory agencies to establish permissible exposure standards.) Chronic feeding studies in dogs[9]

demonstrated increased mortality, decreased food consumption and weight gain, increased liver, ovary and heart weights (in females) with related electrocardiographic changes in the heart accompanied by detectable pathology in both sexes. (The NOEL for these effects was 15 ppm.) Other studies have also demonstrated changes in liver and kidney function.[10,11]

Tests of atrazine's ability to cause cancer in rats using technical atrazine (the active ingredient only, not formulated products) found dose-related breast tumors in females and tumors in the testicles of males.[9] Another rat study found a dose related increase in combined leukemia/lymphoma (cancer of the lymph system) incidence, an increase in benign mammary tumors in males, and an increase in cancer of the uterus in females.[12] Commercial (formulated) atrazine products given by injection under the skin or into the viscera of mice at 2 ppm resulted in the development of lymphomas and mesotheliomas (another cancer).[13]

In humans, use of triazine herbicides has been associated with an increase in tumors of the ovary.[14] Women previously exposed to triazines developed the tumors 2.7 times as frequently as unexposed women. A study of eastern Nebraska residents found that exposure to atrazine was associated with an elevated risk of another cancer, non-Hodgkin's lymphoma.[15] Atrazine is classified by EPA as a possible human carcinogen (Class C) based on the increased incidence of mammary tumors in female rats.[2]

While neither atrazine nor extracts from untreated plants appeared mutagenic, a water soluble extract from maize plants grown in the presence of Aatrex 80W (with active ingredient atrazine) contained a mutagenic agent(s) when tested on strains of yeast.[16] Rats given high oral doses of atrazine suffered DNA lesions in the stomach, kidney, and liver.[17] In addition, field tests with commercial atrazine products have demonstrated genotoxic effects on maize pollen.[18]

Treatment of rat mothers with atrazine and one of its metabolites during pregnancy and nursing resulted in slow maturation of their offsprings' sexual organs. As a consequence, pituitary activity was modified in both male and female offspring, and certain hormone receptors were strongly inhibited.[19]

Treatment of rat mothers with atrazine caused a reduction in the weight of their offspring.[20,21] The NOEL for this effect was 0.5 mg/kg/day. Atrazine also produced a dose-related pattern of toxicity in the mothers, including mortality at high doses and decreases in food consumption, body weight, and body weight gain.[20] The maternal NOEL was estimated to be 10 mg/kg per day. At high doses (700 mg/kg/day) maternal mortality was 78 percent and clinical signs included salivation, bloody vulvae, and swollen abdomens. Rabbits also experienced similar effects: bloody vulvae, reduction in feed consumption, body weight, and body weight gain in mothers. Reduced fetal weights, increased skeletal abnormalities, and increases in embryo loss were associated with this maternal toxicity. The maternal NOEL was 1 mg/kg/day and the fetal NOEL was 5 mg/kg/day.[20]

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